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Treatment of hyperphosphatemia with sevelamer hydrochloride in hemodialysis patients: A comparison with calcium acetate

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Treatment of hyperphosphatemia with sevelamer hydrochloride in hemodialysis patients: A comparison with calcium acetate.

Background. Sevelamer hydrochloride is a recently approved calcium- and aluminium-free phosphate binder. A randomized study comparing sevelamer and calcium acetate was performed to assess the control of hyperphosphatemia in hemodialysis patients.

Methods. Administration of phosphate binders was discontinued during a two-week washout period. The patients were then randomized to receive sevelamer or calcium acetate. The laboratory tests were performed monthly for 34 weeks.

Results. There was a statistically significant decrease of serum phosphorus in both sevelamer and calcium acetate treatments. In addition, sevelamer improved the lipid profile.

Conclusion. This study confirms that sevelamer is effective at lowering serum phosphorus in hemodialysis patients and that it has several striking properties that could be beneficial in atherosclerosis in dialysis patients.

Secondary hyperparathyroidism and hyperphosphatemia are common complications in end-stage renal disease. Treatment usually includes dietary restriction of phosphorus, use of carbonate or acetate salts of calcium, and often, the administration of vitamin D metabolites [1, 2, 3]. Calcium salts have become the treatment choice for hyperphosphatemia, although the provision of calcium can lead to hypercalcemia and increase the risk of metastatic calcification, particularly in those patients on calcitriol therapy and patients with low bone turnover rates [1, 3–5].

Sevelamer hydrochloride is a recently approved calcium- and aluminum-free phosphate binder. In previous studies it effectively controlled serum phosphate in hemodialysis patients without developing hypercalcemia [6].

A randomized study comparing sevelamer and calcium acetate was therefore performed to assess the efficacy of sevelamer in lowering serum phosphorus in hemodialysis patients.

Key words: hyperparathyroidism, hemodialysis, hypercholesterolemia.

METHODS

Patients

The study included male and female hemodialysis patients aged 18 years or older who were treated for at least three months with hemodialysis three times per week. Inclusion criteria required calcium-based phosphate binders and vitamin D therapy at stable doses for at least one month. Furthermore, subjects were excluded from participation if they had any unstable medical condition, including poorly controlled diabetes mellitus, hypertension, or any gastrointestinal abnormality.

Study design

Patients were chosen and administration of calcium-containing phosphate binder was discontinued during a two-week washout period. Patients who developed a serum phosphorus level greater than 6 mg/dL during this washout were eligible for the study. After the two-week washout phase, subjects were randomized to receive sevelamer hydrochloride or calcium acetate. Sevelamer was supplied in a capsule containing 403 mg (Renagel®), while the calcium acetate was supplied as Royen®, containing 500 mg calcium acetate. The beginning medication dose was determined by the initial level of phosphorus and ranged from 2 to 4 capsules three times a day with meals for sevelamer, to 1 to 4 tablets three times per day with meals for calcium acetate [4, 7]. Sevelamer and calcium acetate doses could be increased by one capsule or tablet per meal (three capsules or tablets per day) every four weeks. Serum levels of phosphorus, calcium, alkaline phosphatase, parathyroid hormone (PTH), total cholesterol, HDL-cholesterol, LDL-cholesterol, and other laboratory tests were monitored at the pre-washout period and at weeks 2, 6, 10, 14, 18, 22, 26,

Table 1. Baseline patients' characteristics

N	51
Age *years*	60.4 ± 15.1
Gender *% female*	40%
Primary renal disease	
Glomerulonephritis	17.5%
Interstitial	15%
Cystic	7.5%
Hypertension	15%
DM	15%
Unknown	25%
Others	5%
Length of dialysis *months*	56.9 ± 48.7
Previous phosphate binders	
Calcium acetate	79%
Calcium carbonate	21%
Dialysate calcium *mEq/L*	
2.5	79%
3.0	21%
Parathyroidectomy	10%
Vitamin D metabolites	70%
Kt/V	1.16 ± 0.15
Serum albumine	3.86 ± 0.41
Cholesterol-lowering agents	11.7%

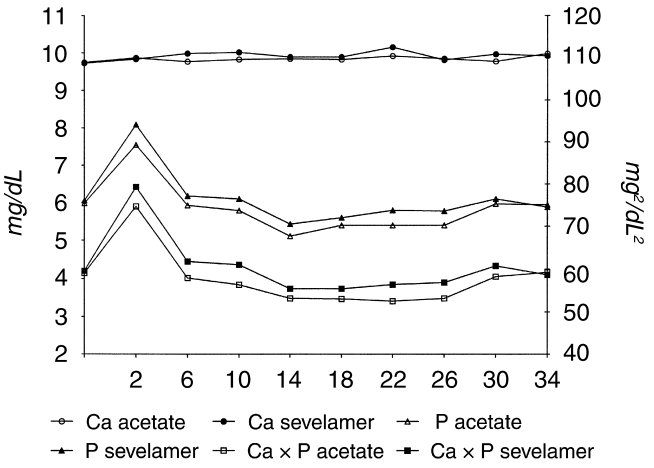

Fig. 1. The trends over time in phosphorus, calcium, and calcium x phosphorus product.

30, and 34 during the treatment period. Laboratory tests were drawn before the mid-week dialysis session.

Statistical analysis

Continuous variables were expressed as mean values ± SD. Baseline characteristics were compared between the two groups of patients using a Fisher exact test for categorical variables and a Wilcoxon signed rank test for continuous variables. The effect of treatment was analyzed by measuring the change from the end of the washout period to the determination of the treatment period by a paired *t* test. An analysis of variance model was used to assess differences between treatment groups. All statistical analyses were two-tailed with a P value of 0.05 required for significance and conducted using a SPSS.10 software package (SPSS, Inc., Chicago, IL, USA) for Windows (Microsoft Corporation, Redmond, WA, USA), and were restricted to subjects who completed the study (N = 40, 78%).

RESULTS

Patients

Sixty-one patients entered the screening period; after a washout period, 51 met the study criteria and were randomized. Forty patients completed the study. Reasons for withdrawal from the study were: four deaths, two kidney transplants, one adverse event (gastric bezoar), and four cases of lack of compliance. Table 1 shows the baseline patients' characteristic. Sevelamer was well tolerated and the occurrence of side effects was similar for each treatment. Dyspepsia occurred during sevelamer treatment in 38% of patients versus 36% during calcium acetate treatment. The incidence of diarrhea, constipation, and other minimal adverse events was not statistically different between groups (P = 0.2). In the sevelamer group, there was one patient with a gastric bezoar who dropped out of the study.

Dosage and dietary intake

For sevelamer, the mean dose given was 4.09 g/day, and for calcium acetate, the mean dose given was 3.9 g/day. Dietary intake of calcium, phosphorus, and vitamin D metabolites remained relatively stable throughout the study and was equivalent between groups.

Serum phosphorus, calcium, alkaline phosphatase, and intact parathyroid hormone

Figure 1 shows the changes in serum calcium, serum phosphorus, and serum calcium x phosphorus product in both the calcium and sevelamer groups. The mean serum phosphorus baseline concentration was not statistically significant before treatment with sevelamer and calcium acetate (8.09 ± 1.6 mg/dL vs. 7.5 ± 1.5 mg/dL; P = 0.5). There was a statistically significant decrease with both treatments that ranged from 8.09 ± 1.6 mg/dL to 5.8 ± 1.01 mg/dL; P = 0.001 for the sevelamer group, and from 7.5 ± 1.6 mg/dL to 5.9 ± 1.5 mg/dL; P = 0.005 for the acetate group. The mean change in serum phosphorus from baseline to the end of treatment was similar between treatments: −2.29 ± 0.05 mg/dL (28.3%) with sevelamer and −1.6 ± 0.1 mg/dL (21.3%) with calcium acetate. There was not a statistically significant increase of serum calcium in either the sevelamer or calcium acetate therapy (Fig. 1). At least one instance of hypercalcemia, defined as a serum calcium greater than 11 mg/dL, occurred in 7.1% (N = 9) of patients with sevelamer treatment, and in 8.9% (N = 15) of patients with calcium acetate treatment (P = 0.2). Al-

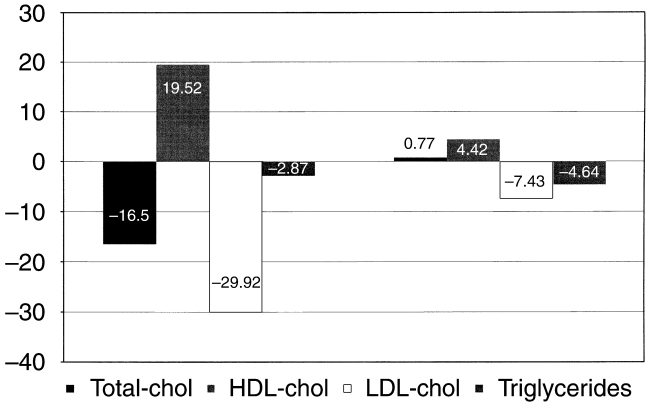

Fig. 2. Percent change in total cholesterol, LDL-Cholesterol, HDL-cholesterol, and triglyceride values.

though the mean baseline calcium x phosphorus product was higher before treatment with sevelamer than calcium acetate (79.3 ± 17.1 mg^2 /dL^2 versus 74.6 ± 18.4 mg^2/dL^2; $P = 0.7$), the mean change from baseline to the end of treatment was similar between treatments (−20.6 mg^2/dL^2) with sevelamer and (−15.4 mg^2/dL^2) with calcium acetate. Intact PTH levels also decreased with both treatments, from 479 ± 288 pg/mL to 330 ± 205 pg/mL; $P = 0.04$ in the sevelamer group, and from 501 ± 303 pg/mL to 346 ± 250 pg/mL; $P = 0.02$ in the calcium acetate group. Serum alkaline phosphatase did not increase significantly with sevelamer treatment (230 ± 78 UI/L to 243 ± 65 UI/L; $P = 0.3$) and did not change significantly with calcium acetate therapy (227 ± 93 UI/L to 226 ± 120 UI/L; $P = 0.9$).

Serum lipids

Figure 2 shows the changes on the lipid profile. For the sevelamer treatment group, the mean change in the total cholesterol was −30.5 ± 13.1 mg/dL (−16.5%), LDL-cholesterol was −32.8 ± 14.5 mg/dL (−29.9%), and HDL-cholesterol was 8.2 ± 4.6 mg/dL (19.5%). All values were statistically significant at $P < 0.05$. For the calcium acetate treatment group, the mean levels of total cholesterol, LDL-cholesterol and HDL- cholesterol were not significantly changed.

In both treatments, other laboratory values such as triglycerides, serum albumin, total protein, liver enzymes, and bilirubin were not significantly changed.

DISCUSSION

The efficacy of currently available calcium- or aluminum-containing phosphate binders is constrained by the side effects associated with the absorption of calcium and aluminum. Aluminum absorption can lead to toxicity in some patients [8–13], and calcium carbonate or calcium acetate can lead to hypercalcemia in some patients [1, 3, 5, 14, 15].

We explored the use of a recently approved calcium- and aluminum-free phosphate binder to lower serum phosphorus levels in hemodialysis patients and compared it with a standard therapy on a similar population.

This long-term study confirms previous reports, in which sevelamer is effective at lowering serum phosphorus in hemodialysis patients [4, 7, 16–19]. Serum phosphorus was significantly reduced by both sevelamer and calcium acetate treatments, with a corresponding reduction in the calcium x phosphorus product. This beneficial effect was sustained over time. The serum phosphorus levels achieved at the end of the study was similar to that observed in other clinical trials. The intact PTH decreased significantly in both sevelamer and calcium acetate treatments, but it did not achieve the normal range in dialysis patients at the end of the study. Perhaps the reasons for not achieving optimal levels of both serum phosphorus and intact PTH were that the dose of sevelamer was sub-optimal (the mean dose given was 4.09 g/day). The limitation in our patients was the need for taking a high number of capsules. Recently, the suitability of sevelamer has been improved with new 800 mg tablets.

Serum calcium was slightly, but not significantly, increased in sevelamer treatment. Because sevelamer decreases serum phosphorus with the ability to avoid hypercalcemia, we found a subsequent reduction in calcium x phosphorus product. This is probably the most important sevelamer benefit. Block et al [20] recently pointed out an increase in the relative risk of death with higher levels of calcium x phosphorus product. Other authors have also hypothesized that higher levels of the calcium x phosphorus product might promote vascular calcification and lead to a decrease in survival related to cardiovascular disease [16]. Coronary-artery calcification is common and progressive in young adults who are undergoing dialysis [21, 22]. There is evidence that an effective phosphate lowering with sevelamer is associated with less coronary and aortic calcification [23].

The mild increase in serum alkaline phosphatase during sevelamer treatment was most likely related to its effects on bile acid metabolism [7, 16].

CONCLUSION

Sevelamer treatment reduced both serum total cholesterol and LDL-cholesterol. The 29% reduction in LDL-cholesterol by sevelamer treatment is similar to the reduction obtained by cholesterol-lowering agents [24, 25]. Nevertheless, alternatives to HMG-CoA reductase inhibitors may be advisable, given the increased risk of drug-related side effects in patients with chronic renal failure [18]. In addition, sevelamer treatment signifi-

cantly increases HDL-cholesterol [16], or has no effect at all [7, 18, 19]. The relative benefits of modifying the lipid profile in hemodialysis patients are also unknown. Levels of serum cholesterol at both extremes were associated with an increased risk of death in a large cohort of hemodialysis patients [16, 18, 26]. Currently, atherosclerosis is accelerated by as much as 20 years in dialysis patients compared to the general population [27], and the risk of myocardial ischemia and infarction is increased in patients with ESRD, compared with nonuremic age- and sex-matched individuals [28]. Changes in LDL-cholesterol and HDL-cholesterol induced by sevelamer in this study would be expected to reduce the rate of cardiovascular disease, and potentially increase survival in these patients. Whether there might be an additive or synergic effect of modifying the lipid profile and lowering calcium x phosphate product is still unknown [16].

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